AMERICAN ACADEMY OF NEUROLOGY

Special Article

Practice Parameter: Prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

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Abstract—*Objective:* To systematically review outcomes in comatose survivors after cardiac arrest and cardiopulmonary resuscitation (CPR). *Methods:* The authors analyzed studies (1966 to 2006) that explored predictors of death or unconsciousness after 1 month or unconsciousness or severe disability after 6 months. *Results:* The authors identified four class I studies, three class II studies, and five class III studies on clinical findings and circumstances. The indicators of poor outcome after CPR are absent pupillary light response or corneal reflexes, and extensor or no motor response to pain after 3 days of observation (level A), and myoclonus status epilepticus (level B). Prognosis cannot be based on circumstances of CPR (level B) or elevated body temperature (level C). The authors identified one class I, one class II, and nine class III studies on electrophysiology. Bilateral absent cortical responses on somatosensory evoked potential studies recorded 3 days after CPR predicted poor outcome (level B). Burst suppression or generalized epileptiform discharges on EEG predicted poor outcomes but with insufficient prognostic accuracy (level C). The authors identified one class I, 11 class III, and three class IV studies on biochemical markers. Serum neuron-specific enolase higher than 33 μg/L predicted poor outcome (level B). Ten class IV studies on brain monitoring and neuroimaging did not provide data to support or refute usefulness in prognostication (level U). *Conclusion:* Pupillary light response, corneal reflexes, motor responses to pain, myoclonus status epilepticus, serum neuron-specific enolase, and somatosensory evoked potential studies can reliably assist in accurately predicting poor outcome in comatose patients after cardiopulmonary resuscitation for cardiac arrest.

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Despite improving resuscitation practices, the outcome of most patients after a cardiac arrest remains poor. Overall, out-of-hospital cardiopulmonary resuscitation (CPR) for cardiac arrest has a success rate of <10%.[1] Even when patients are resuscitated in the hospital, fewer than one in five patients survive to discharge.[2] When pulse and blood pressure return after CPR, the brain may have already been critically injured. When severe, a postresuscitation anoxic-ischemic encephalopathy leaves patients comatose. Awakening generally takes place within 3 days after CPR, and neurologic impairment is ex-

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pected if a patient fails to do so.[3-5] These patients are often left in a severely cognitively disabled and fully dependent state; some remain in a minimally conscious or vegetative state, and very few awaken neurologically intact. The financial implications of caring for patients in a vegetative state or prolonged impaired consciousness are substantial. Health systems and family members directly are burdened by the considerable costs of permanent or extended periods of nursing home care.[6]

Discussions about the level of care—continuing intensive care or withdrawal of life sustaining support—may start as early as the day of admission and are many times motivated by a neurologic consultation. Neurologists make a key contribution in the assessment of comatose patients and the direction of level of care. First, neurologists are expected to provide accurate prognostic information: will the patient awaken, and, if so, in what neurologic state? Second, neurologists are expected to communicate the findings to family members, regrettably, often to announce grave seriousness of the patient's condition. If the probability of devastating neurologic disability is high, family members or proxy may prefer no further resuscitation, no surgical interventions, or the withdrawal of critical care. When instructed by the patient's prior written advance directives, others may quickly opt to limit care to comfort measures alone.

The assessment of neurologic prognosis has long been based mainly on the algorithms of Levy et al.,[3] which derive from a single cohort study and brings about substantial statistical uncertainty. In developing practice parameters, it is important to consider all the available evidence, to assess its validity, and to provide an estimate of the accuracy of independent predictors. This is particularly opportune because new prospective data have been published[7-10] since the article by Levy et al.

An international group was formed to review the prognostic value of the clinical examination and of ancillary investigations (electrophysiologic, biochemical, and radiologic) for poor outcome in comatose survivors after CPR. We specifically assessed the value of the following seven variables to predict poor outcome: Circumstances surrounding CPR, elevated body temperature, neurologic examination, electrophysiologic studies, biochemical markers, monitoring of brain function, and neuroimaging studies.

Description of the analytical process. *Literature search.* The Mayo Clinic Library and the Biomedical Library Information Service of the University of Minnesota searched MEDLINE from January 1966 to January 2006. Review articles and monographs were additionally consulted. Search entries included the following text words and MeSH terms associated with cardiorespiratory resuscitation: "coma," "anoxic encephalopathy," "prognosis," "electrophysiological studies," and "biochemical markers."

Selection of studies. We excluded studies in which coma was not adequately described, single case reports, papers dealing with selected subgroups of patients, and papers written in a language other than English, German, French, or Italian or when an English translation was not available. Selected articles fulfilled the following inclusion criteria: documented cardiac arrest, age ≥17 years, and we accepted the following definitions of coma: Glasgow Coma Scale score sum score ≤8, "persistent unresponsiveness," and "not regaining consciousness." Poor outcome was defined as 1) death or persisting unconsciousness after 1 month or 2) death, persisting unconsciousness, or severe disability requiring full nursing care after 6 months. We chose these outcome measures because the chance of survival without severe motor or cognitive disability is virtually nil in patients who are vegetative ≥1 month or more after CPR or in patients who are severely disabled after ≥6 months.

We obtained 391 potentially eligible literature citations that were reviewed in full by members of the practice parameter group. We additionally reviewed authoritative position papers on permanent vegetative state,[11] withdrawal of care in the intensive care unit,[12] and communication with the family.[13]

Rating and assessment of studies. Four class I studies,[3,7,10,14] three class II studies,[15-17] and five class III[18-22] studies were reviewed on circumstances surrounding CPR and clinical features.

One class I study,[7] one class II study,[23] and nine class III studies[17,19,24-30] were reviewed on electrophysiologic studies. One class I study,[7] 11 class III studies,[22,31-40] and three class IV studies[41-43] were reviewed on biochemical markers.

Ten class IV studies were reviewed on monitoring brain function and neuroimaging.[44-53]

Recommendations were graded according to the American Academy of Neurology evidence classification scheme for rating of a prognostic article, established by the Quality Standards Subcommittee (see appendixes 2 and 3). The reviewed studies are summarized in evidence tables. We used opinion papers and expert opinion to formulate suggestions to communicate with family members.

Statistical analysis and calculations. When data could be abstracted from the articles, we calculated sensitivity, false-positive rate (FPR) (1 – specificity), and corresponding 95% CI. We chose to report our calculation of the FPR because clinicians need to be informed about the ability of the clinical examination and laboratory tests to predict poor outcome with a high level of certainty (low FPR). We calculated 95% CIs for sensitivity and FPR using Wilson's method, as recommended by Altman et al.[54] For meta-analyses, we assessed heterogeneity with the χ^2 test. In the absence of heterogeneity, we used the fixed-effects method to pool the data.[54]

Results and recommendations. *Are the circumstances surrounding CPR predictive of outcome?* Evidence. One class I study[14] has documented differences between patients with poor and those with good outcomes for anoxia time (time between collapse and initiation of CPR), duration of CPR, cause of the cardiac arrest (cardiac vs noncardiac), and type of cardiac arrhythmia (ventricular fibrillation or tachycardia vs asystole or electro-mechanic dissociation) (appendix E-1). The FPR of these variables was unacceptably high, ranging from 20 to 27% with narrow CIs.

Conclusions. Anoxia time, duration of CPR, and cause of cardiac arrest are related to poor outcome after CPR, but none of these variables can discriminate accurately between patients with poor and those with favorable outcomes.

Recommendations. Prognosis cannot be based on the circumstances of CPR (recommendation level B).

Is hyperthermia predictive of outcome? Evidence. One class II study[15] reported an association between elevated body temperature (measured with tympanic thermometry within the first 48 hours) and associated poor outcome. For each degree Celsius above 37 °C, patients were 2.26 times more likely to die or remain in a vegetative state after 6 months. However, patients with poor outcome cannot be identified

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with body temperature measurements alone.

Conclusions. Elevated body temperature (>37 °C) is associated with poor outcome. However, hyperthermia alone could not discriminate accurately between patients with poor and those with favorable outcomes.

Recommendations. Prognosis cannot be based on elevated body temperature alone (recommendation level C).

Which features of the neurologic examination of the comatose patient are predictive of outcome? The predictive value of the Glasgow Coma Scale (GCS) score, the motor part of the GCS, brainstem reflexes (pupillary light reflexes, corneal reflexes, and eye movements), and the presence of seizures or myoclonus status epilepticus have been investigated in three class I studies,[3,7,10] two class II studies,[16,17] and five class III studies[18-22] (appendix E-1). Because most patients are intubated in the first few days after CPR, and eye opening to pain may occur early in the course without implying a favorable prognosis, the motor component of the GCS score is more useful and accurate than the GCS sum score.[3] False-positive predictions of poor outcome may occur with a GCS motor score <2 (i.e., extensor or absent motor responses) 24 to 48 hours after CPR, but no false predictions occurred after 72 hours[3,7,10] (FPR = 0, 95% CI: 0 to 6). Similarly, there were no false predictions of poor outcome for absent pupillary light reflexes 24 to 72 hours after CPR, absent corneal reflexes after 3 days, and absent eye movements (i.e., no spontaneous eye movements and absent oculocephalic reflexes) after 3 days, but the long CIs concerning eye movements reduces their prognostic reliability. (appendix E-1). Overall, at 72 hours, a GCS motor score ≤2 or absence of brainstem reflexes had a 0 FPR (95% CI: 0 to 3). Single seizures and sporadic focal myoclonus do not accurately predict poor outcome.[7,19] In contrast, in one class I study[7] and one class III study,[20] myoclonus status epilepticus (defined as spontaneous, repetitive, unrelenting, generalized multifocal myoclonus involving the face, limbs, and axial musculature in comatose patients) was invariably associated with in-hospital death or poor outcome, even in patients with intact brainstem reflexes or some motor response. Myoclonus status epilepticus may be only present on the day of CPR or may not be noted. This may explain the major discrepancy in reported prevalence.[7,19,20] In our meta-analysis, FPR was 0% (95% CI: 0 to 8.8) for poor outcome associated with myoclonus status epilepticus on day 1. In one class IV postmortem study,[55] this condition was associated with severe ischemic brain, brainstem, and spinal cord damage. Myoclonus status epilepticus has been reported with patients surviving only with severe disability including persistent vegetative state.[7,20,56] Incidental cases have been described with good recovery,[57-60] mainly in patients in whom circulatory arrest was secondary to respiratory failure. In some of these cases, accumulation of sedative agents could have been confounders, and in others, myoclonus may not have been generalized, persistent, and merely sporadic.

Conclusions. The following clinical findings accurately predict poor outcome (FPR of 0 with narrow CIs); myoclonus status epilepticus within the first 24 hours in patients with primary circulatory arrest, absence of pupillary responses within days 1 to 3 after CPR, absent corneal reflexes within days 1 to 3 after CPR, and absent or extensor motor responses after 3 days.

Recommendations. The prognosis is invariably poor in comatose patients with absent pupillary or corneal reflexes, or absent or extensor motor responses 3 days after cardiac arrest (recommendation level A). Patients with myoclonus status epilepticus within the first day after a primary circulatory arrest have a poor prognosis (recommendation level B).

Which electrophysiologic studies are helpful in determining outcome? Electrophysiologic tests in coma consist of EEG and evoked/event-related potential (EP) studies.

Evidence. The EEG literature is confounded by different classification systems and variable intervals of recordings after CPR. In most studies, EEG categories have been collapsed into two categories to allow for comparisons and statistical analyses: malignant and benign or uncertain. Most malignant categories include suppression, burst-suppression, alpha and theta pattern coma, and generalized periodic complexes combined; hence, the predictive value of individual classifications has not been adequately addressed. This represents a condensation of the categories contained in several proposed classification systems.[24,61,62]

Published EEG series include one class II study[23] and four class III studies[19,24-26] (appendix E-2). Most studies report intervals from CPR to EEG recording of <3 days, but there is considerable variation. Complete suppression (isoelectric EEG) or burst-suppression patterns containing generalized epileptiform discharges may have predictive ability for outcomes, but these have rarely been examined separately. Generalized suppression to ≤20 μV, burst-suppression pattern with generalized epileptiform activity, or generalized periodic complexes on a flat background are associated with outcomes no better than persistent vegetative state.[63,64] The so-called alpha-coma pattern does not invariably herald a poor outcome.[17,65,66] Serial or continuous EEGs may appear more accurate and valid than single EEGs, but this remains to be adequately tested.[67] The presence of EEG reactivity and variability has been suggested to favorably predict recovery of consciousness, but this has not been independently demonstrated.[64,65] In our meta-analyses of studies reporting malignant EEG patterns, the FPR for poor outcome was 3% (95% CI: 0.9% to 11%).

Conclusions. Generalized suppression to ≤20 μV, burst-suppression pattern with generalized epileptiform activity, or generalized periodic complexes on a flat background are strongly but not invariably associated with poor outcome.

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Recommendations. Burst suppression or generalized epileptiform discharges on EEG predicted poor outcomes but with insufficient prognostic accuracy (recommendation level C).

Evidence. Somatosensory evoked potentials (SSEPs) are much less influenced by drugs and metabolic derangements and are therefore more accurate than EEG in prognostication. One class I study[7] and seven class III studies[17,19,26-30] (appendix E-3) were identified. Bilateral absence of the N20 component of the SSEP with median nerve stimulation had good predictive value for poor outcome with all but one study showing FPRs of 0%. One class I study and all but one class III studies demonstrated FPRs of 0%. Our meta-analyses data from eight studies demonstrated an FPR of 0.7% for poor outcome (95% CI: 0.1 to 3.7) when bilateral absence of N20 response was recorded. Uncertainty remains about the optimal timing of SSEP testing. The N20 responses may disappear on repeat tests after showing initial preservation after cardiac arrest.[68] The intervals from CPR to testing of SSEP vary widely among studies (from hours to many days), but all studies were done within 3 days. A few patients have been reported in whom an absent N20 response > 24 h after CPR was regained later, all with a poor outcome.[7] Conversely, the presence of the N20 response is not helpful in predicting outcome as reflected in a pooled sensitivity of only 46%; many patients who fail to recover will have preserved N20 responses.

Other evoked (brainstem auditory and visual) and event-related potential tests have not been thoroughly tested for their prognostic value in anoxic-ischemic encephalopathy.[69] In one class III study, the middle latency auditory evoked response was absent in all 13 patients who died or remained in a persistent vegetative state (sensitivity 34% [95% CI: 19% to 49%], FPR = 0%).[28]

Although it has been suggested that the presence of later responses (N35 and N70) predicts outcome, this has been insufficiently examined. Whether the preservation of responses to multiple event–related or cognitive event–related potentials may prove useful in indicating favorable outcomes is yet unclear.[70]

Conclusions. Bilateral absence of the N20 component of the SSEP with median nerve stimulation recorded on days 1 to 3 or later after CPR accurately predicts a poor outcome.

Recommendations. The assessment of poor prognosis can be guided by the bilateral absence of cortical SSEPs (N2O response) within 1 to 3 days (recommendation level B).

Do biochemical markers accurately predict outcome? Evidence. Studies have investigated serum neuron-specific enolase (NSE) and serum S100 as markers of brain damage. NSE is a gamma isomer of enolase that is located in neurons and neuroectodermal cells. S100 protein is a calcium-binding astroglial protein. Group analyses have shown that serum levels of NSE, but not those of S100, are significantly lower in patients treated with induced hypothermia compared with those of untreated patients.[31]

One class I study,[7] four class III studies,[22,31-33] and one class IV study[41] have investigated the usefulness of increased serum NSE as a marker of poor outcome (appendix E-4). In the class I study,[7] 60% of 231 patients had NSE >33 μg/L at day 1 to 3 after CPR. All these patients had a poor outcome (FPR of 0, 95% CI: 0 to 3). Most other studies also found an increase in serum NSE at day 3. However, the cutoff points for a 0 FPR value vary greatly (20 to 65 μg/L). An FPR could not be obtained in two studies, and it ranged from 0 to 11% in five class III studies.

Serum astroglial S100 has been investigated in one class I study,[7] four class III studies,[22,31,33,34] and one class IV study.[42] The median FPR was 2% (range 0 to 54%) in the four studies that allowed this calculation, and it was 5% in the class I study. Predictions were based on values measured within the first 2 days after cardiac arrest. Therefore, serum S100 remains a poor prognostic indicator.

Creatine kinase brain isoenzyme (CKBB) is present in neurons and astrocytes. Six class III studies[35-40] investigated the usefulness of CSF CKBB as an indicator of poor outcome. Values used to identify those with poor outcome varied widely. The median FPR was 15% (range 0 to 33%) in six studies allowing the calculations, indicating a poor prognostic ability. Furthermore, the availability of this test result could have influenced the decision to withdraw life support.

Neurofilament in CSF was measured in one class IV study[43] 2 to 3 weeks after resuscitation in a series of 22 patients and yielded an FPR of 10%.

Conclusions. Serum NSE, S100, and CSF CKBB have been investigated as a predictor for outcome with studies using variable cutoff points. For serum NSE levels >33 μg/L at days 1 to 3, one class I study demonstrates a 0 FPR with narrow 95% CIs.

Recommendations. Serum NSE levels >33 μg/L at days 1 to 3 post-CPR accurately predict poor outcome (recommendation level B). There are inadequate data to support or refute the prognostic value of other serum and CSF biochemical markers in comatose patients after CPR (recommendation level U).

Does monitoring of intracranial pressure and brain oxygenation predict outcome? Evidence. The development of cytotoxic edema leads to brain swelling. Further injury results from increased intracranial pressure (ICP) and reduced cerebral perfusion pressure. ICP >20 mm Hg in comatose patients has been associated with poor outcome in one class IV study.[44] Two class IV studies[45,46] have suggested prognostic value of brain oxygenation (using oximetric jugular catheters). One class IV study[45] suggested the oxygen glucose index predicted recovery of consciousness (appendix E-5).

Conclusions. The prognostic usefulness of monitoring of brain oxygenation and ICP is inconclusive.

Recommendations. There are inadequate data to

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support or refute the prognostic value of ICP monitoring (recommendation level U).

Are neuroimaging studies indicative of outcome? Evidence. A noncontrast CT scan is often used to exclude a primary catastrophic brain injury that could result in cardiac arrest and coma. CT scans performed soon after primary cardiac arrest are typically normal, but diffuse brain swelling may occur as early as 3 days after CPR. On CT, an inversed gray/white matter ratio in Hounsfield units was found in patients who failed to awaken after cardiac resuscitation.[47] Seven class IV studies[47-53] assessed the ability of nuclear magnetic resonance spectroscopy, CT, and MRI to identify comatose patients with poor outcome after CPR. Three class IV studies on MRI, selected based on the feasibility and safety to transport patients, have suggested no value of conventional MRI but suggested poor prognosis in patients with diffuse cortical signal changes on diffusion-weighted imaging (DWI) or fluid-attenuated inversion recovery (FLAIR).[52,53] Two class IV studies found no prognostic value in PET studies[48,49] (appendix E-6). (In one study, it was unclear how many children were included and results may not be applicable to this practice parameter.[51])

Conclusions. Brain swelling on CT scanning may occur, but its predictive value for poor outcome is not known. The experience with MRI (DWI and FLAIR) as a tool for prognostication in comatose patients after CPR is limited. There is insufficient evidence to precisely delineate lesions on MRI or CT scanning that would conclusively predict poor outcome.

Recommendations. There are inadequate data to support or refute whether neuroimaging is indicative of poor outcome (recommendation level U).

Confounding factors in prognostication. After CPR, patients are at risk of ischemic damage to multiple organs (postresuscitation injury). Acute renal failure, liver failure, and shock may confound a clinical neurologic examination. Patients may be in cardiogenic shock requiring inotropic agents, may have major metabolic derangements such as a severe metabolic acidosis and other significant organ failure as a result of resuscitation for cardiac standstill. Patients may have received sedatives or neuromuscular blocking agents or induced hypothermia therapy. These therapies and other evidence of organ failure may render prognostic indicators uncertain. However, studies in comatose patients have not systematically addressed the role of these confounders in neurologic assessment.

Timely availability of laboratory tests. SSEPs remain the most valuable laboratory test. The technical procedure and validity of SSEPs can be found in a textbook.[71] The potentials (N20) of interest require documentation at the brachial plexus level and at the cervical cord to be reliably absent. Interpretation of neurologic examination and electrophysiologic tests requires substantial expertise. Timely availability of SSEP recording and interpretation may differ from hospital to hospital. The measurement of NSE is not an automated test and therefore time-consuming, not readily available, and not standardized. However, one study[22] from Germany claimed serum NSE test results could be available within 24 hours. In addition, NSE is present in platelets, and, therefore, hemolysis increases the serum values. MRI or CT scanning in critically ill patients requires displacement out of a controlled supervised environment. In one study,[52] 17 of 27 (63%) patients could not be safely transported to the radiology suite to undergo MRI.

Communication with family and further decision making. The complexity of evaluation and various options of decision making require neurologic professional expertise. The usefulness of the most important prognostic variables in comatose patients after cardiac arrest is summarized in the figure.

Communication with the family or proxy is desired. The neurologist must appreciate that all involved are subsumed by the sudden confrontation of persistent coma despite successful resuscitation, and family members are eagerly awaiting the moment to discuss more details and eventual prognosis. Most families clearly understand the dire situation of a patient who fails to respond and awaken after becoming stable. More than one scheduled meeting with the family is generally required to facilitate a trusting relationship. Exemplary models have been reported that include compassionate communication, encouragement of emotions, and appreciation of personal values and religious preferences.[13] The neurologist can explain that the prognosis is largely based on clinical examination with some help from laboratory tests. In a conversation with the family, the neurologist may further articulate that the chance of error is very small. Poor outcome is explained to them as a severely disabled state with only fragments of understanding, both requiring long-lasting or indefinite comprehensive nursing care. A vegetative state (no awareness of self and environment using a series of stimuli) after CPR may take 1 month to become fully apparent and is permanent if no change after 3 months is observed. Hope for significant recovery is unrealistic, with recovery extremely rare and not better than a severely disabled, fully dependent state of living.[11]

When a poor outcome is anticipated, the need for life supportive care (mechanical ventilation, use of vasopressors or inotropic agents to hemodynamically stabilize the patient) must be discussed. Fully informed and more certain, the family or proxy is allowed to rethink resuscitation orders or even to adjust the level of care to comfort measures only. However, these decisions should be made after best interpretation of advance directives or the previously voiced wishes of the patient.

Measures that can follow are extubation, discon-

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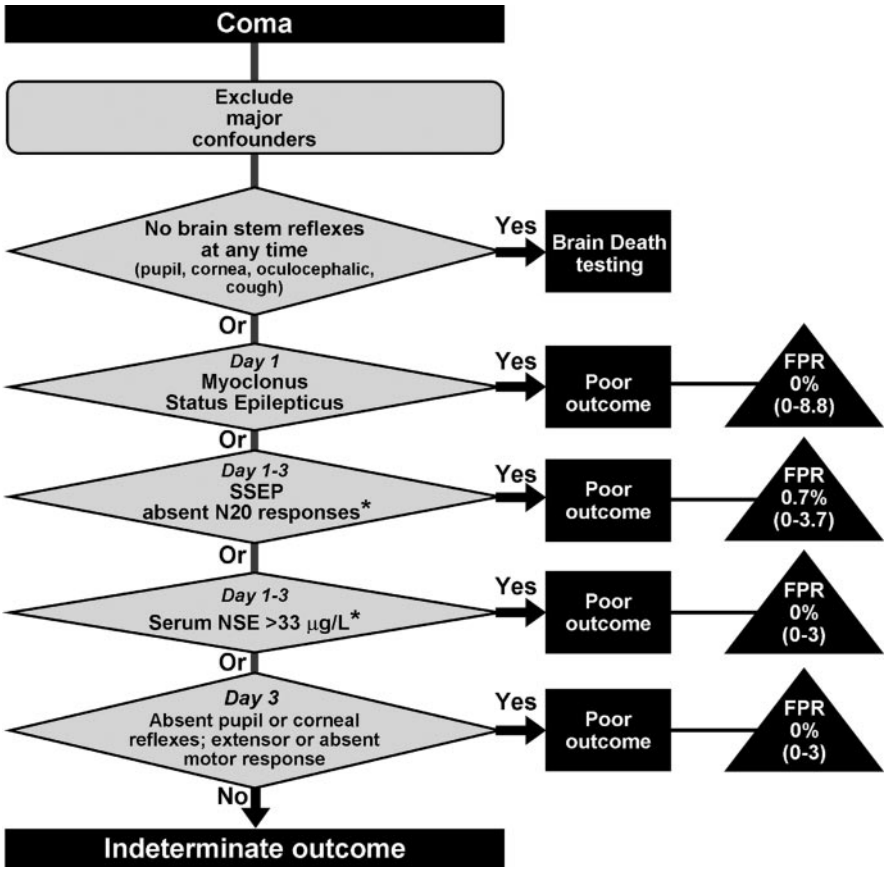

*Figure. Decision algorithm for use in prognostication of comatose survivors after cardiopulmonary resuscitation. The numbers in the triangles are percentages. The numbers in parentheses are exact 95% CIs. Major confounders could include the use or prior use of sedatives or neuromuscular blocking agents, induced hypothermia therapy, presence of organ failure (e.g., acute renal or liver failure) or shock (e.g., cardiogenic shock requiring inotropes). Studies in comatose patients after CPR have not systematically addressed the impact of these factors on the reliability of clinical neurologic examination and tests. Therefore, these confounding factors potentially could diminish the prognostic accuracy of this algorithm. *These test results may not be available on a timely basis. Serum NSE testing may not be sufficiently standardized.*

tinuation of drugs such as inotropic agents, and discontinuation of IV fluid and nutrition. The monitor will be turned off. The family should be told that cardiac arrest is expected soon after extubation, but an irregular breathing pattern and pulse may persist for days. Most patients die peacefully. Further details on end-of-life care in patients admitted to the intensive care unit can be found elsewhere.[11]

Recommendations for future research.

1. Current indicators of poor prognosis in comatose survivors are derived from patients not treated with induced moderate hypothermia. If this treatment becomes standard care, these indicators may need revision. Studies investigating new therapies should specifically record these indicators and correlate them with standard outcome rating scales.

2. The feasibility, costs, and predictive value of MRI (particularly DWI sequences) in determining outcome in patients without certain clinical, electrophysiologic, or biochemical indicators of poor outcome should be further studied.

3. Future studies on outcome are needed. Comprehensive neurologic examination data are still needed. All studies on prognostication are susceptible to "self-fulfilling prophecy." This is a situation in which a physician's negative expectation or overreliance on laboratory tests affects management decisions and thus outcome. Therefore, it is paramount that studies adhere strictly to independent assessment of prognostic indicators and outcomes. It is important to describe causes of death (e.g., cardiac arrhythmias, ventricular rupture, brain death due to brain swelling) and the role of withdrawal of support in patients who died. Long-term outcome (1 year) of survivors is needed with detailed assessment of disability.

4. Further investigation of combined use of middle and late components of the auditory evoked responses may help to identify those with poor outcomes in those comatose patients in whom the N20 response on SSEPs is maintained.

Mission statement. The mission of the QSS is to prioritize, develop, and publish evidence-based practice parameters related to the diagnosis, treatment, and prognosis of neurologic disorders. The QSS is committed to using the most rigorous methods available within our budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

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physician caring for the patient, based on all the circumstances involved.

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Appendix 1

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Appendix 2

American Academy of Neurology evidence classification scheme for rating of a prognostic article

Class I: Evidence provided by a prospective study of a broad spectrum of persons who may be at risk for developing the outcome (e.g. target disease, work status). The study measures the predictive ability using an independent gold standard for case definition. The predictor is measured in an evaluation that is masked to clinical presentation, and the outcome is measured in an evaluation that is masked to the presence of the predictor. All patients have the predictor and outcome variables measured.

Class II: Evidence provided by a prospective study of a narrow spectrum of persons at risk for having the condition, or by a retrospective study of a broad spectrum of persons with the condition compared to a broad spectrum of controls. The study measures the prognostic accuracy of the risk factor using an acceptable independent gold standard for case definition. The risk factor is measured in an evaluation that is masked to the outcome.

Class III: Evidence provided by a retrospective study where either the persons with the condition or the controls are of a narrow spectrum. The study measures the predictive ability using an acceptable independent gold standard for case definition. The outcome, if not objective, is determined by someone other than the person who measured the predictor.

Class IV: Any design where the predictor is not applied in an independent evaluation OR evidence provided by expert opinion or case series without controls.

Appendix 3

Classification of recommendations

A = Established as effective, ineffective, or harmful for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)

B = Probably effective, ineffective, or harmful for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, predictor is unproven.

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